Lipoprotein Metabolism and Atherosclerosis

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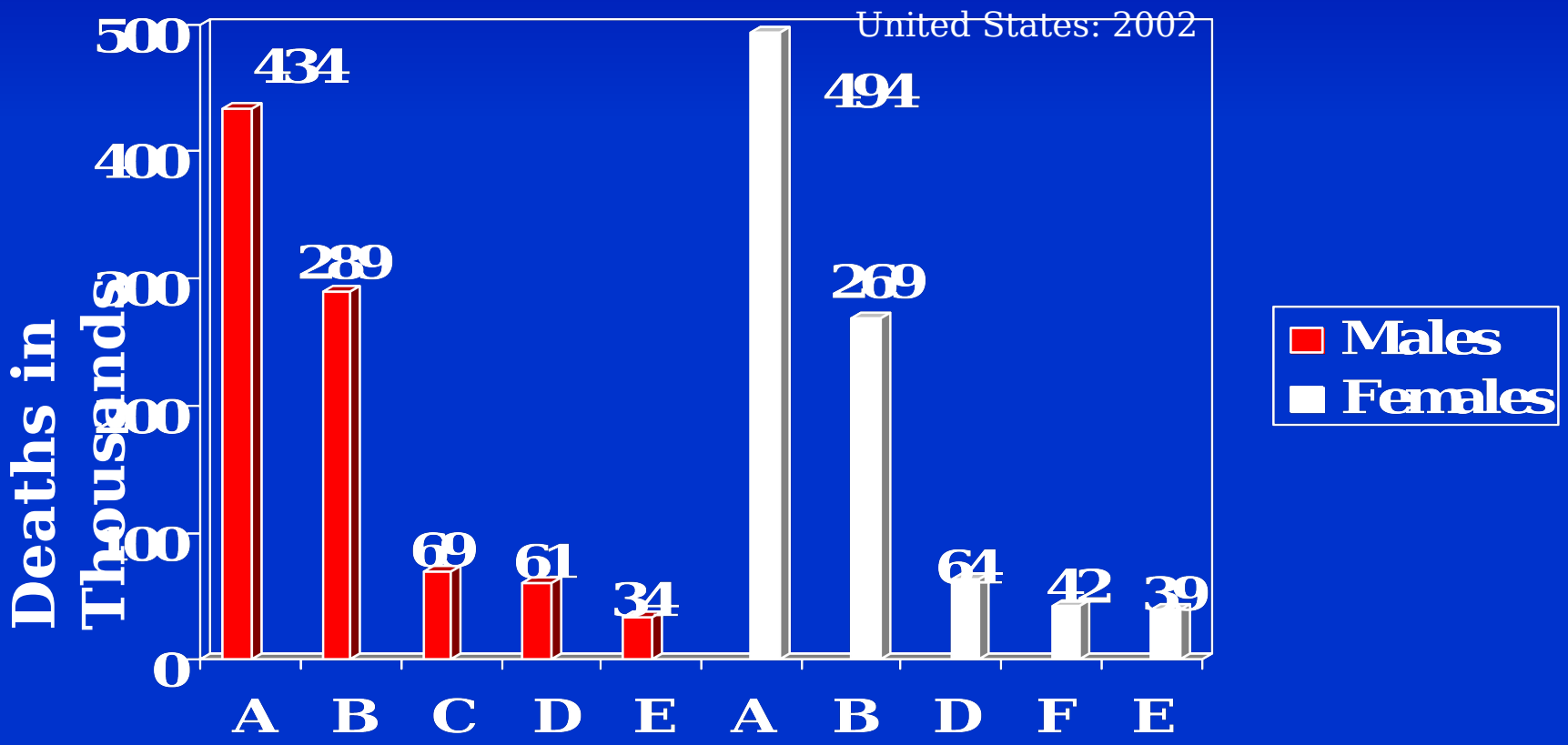
Lipoprotein Metabolism Section

Leading Causes of Death for Males and Females

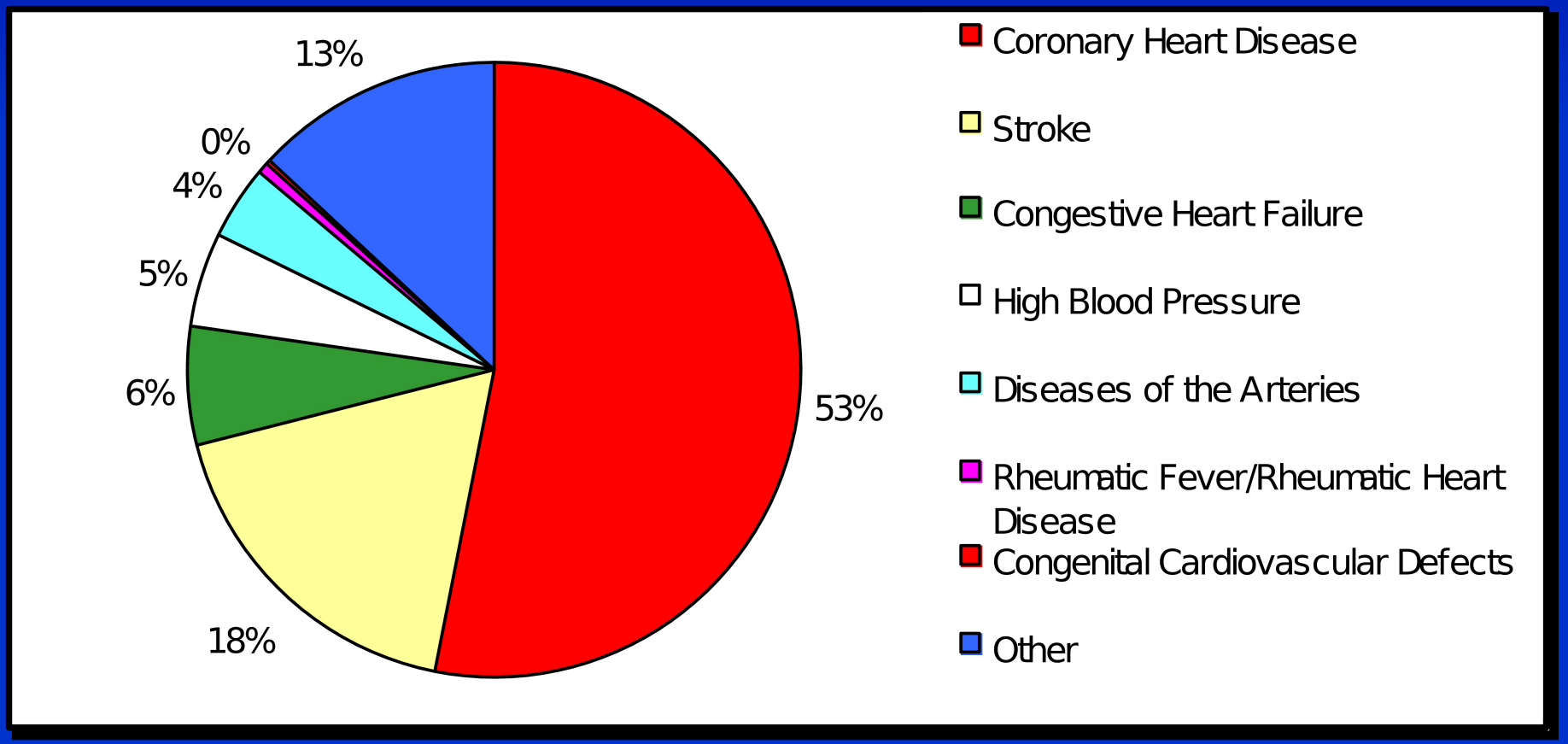


A- Total CVD
B- Cancer
C- Accidents
D- Chronic Lower Resp. Diseases
E- Diabetes Mellitus
F- Alzheimer's Disease

Source:

Percentage Breakdown of Deaths From Cardiovascular Diseases

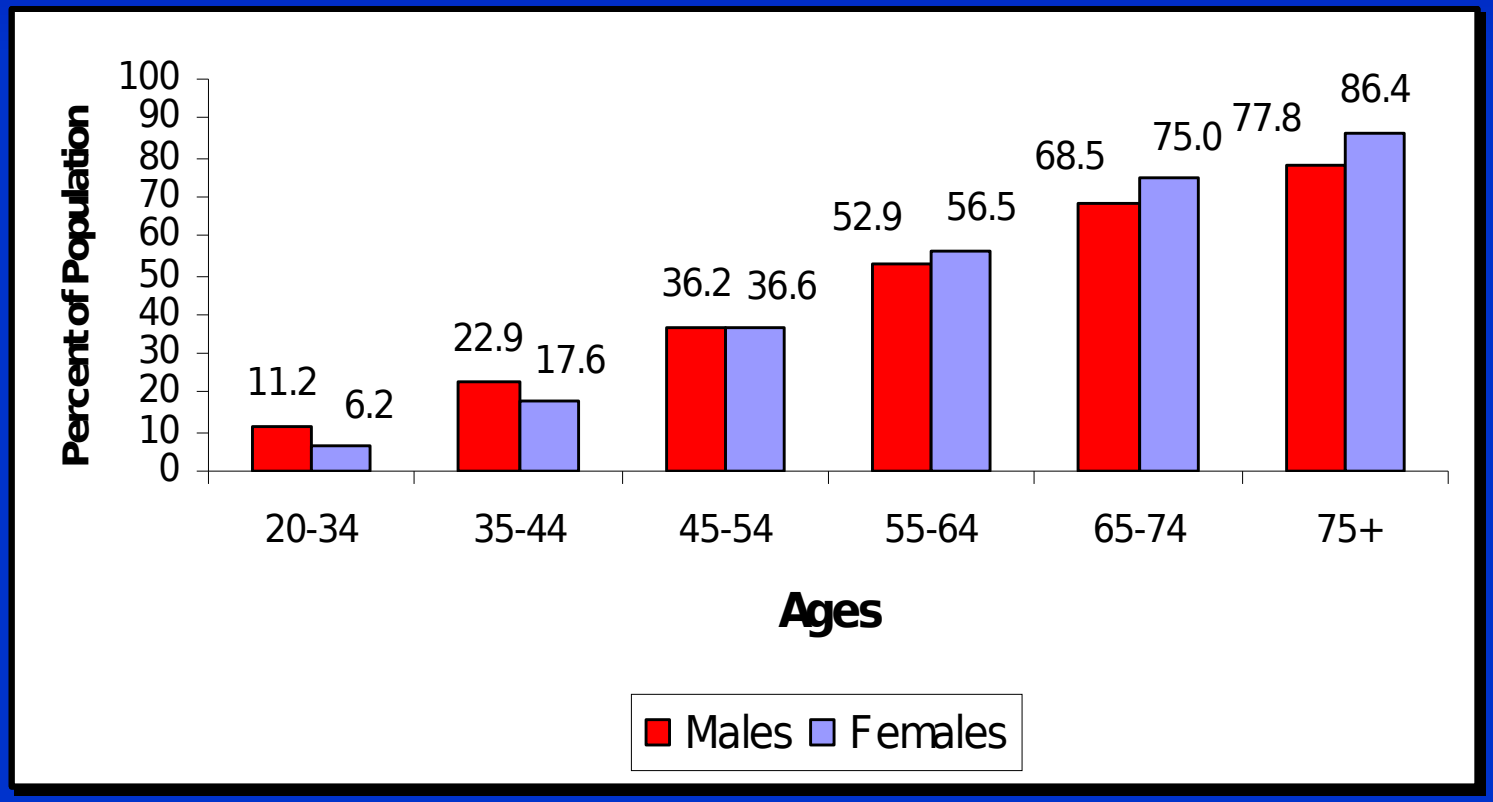
United States:2002 Preliminary



Source: CDC/NCHS.

Prevalence of Cardiovascular Diseases in Americans Age 20 and Older by Age and Sex

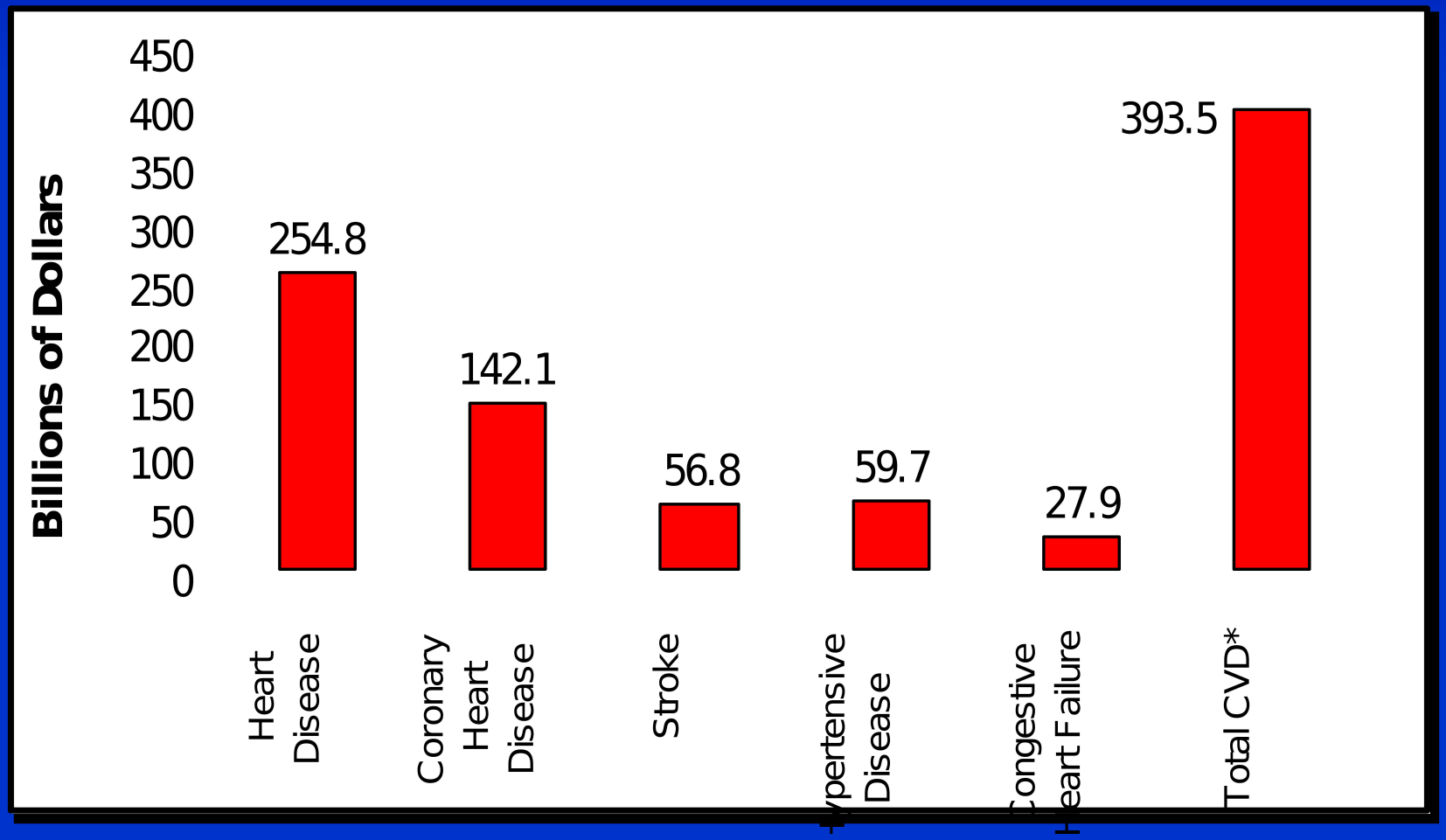
NHANES: 1999-2002



Source: CDC/NCHS and NHLBI. These data include coronary heart disease, congestive heart failure, stroke and hypertension.

Estimated Direct and Indirect Costs of Cardiovascular Diseases and Stroke

United States: 2005

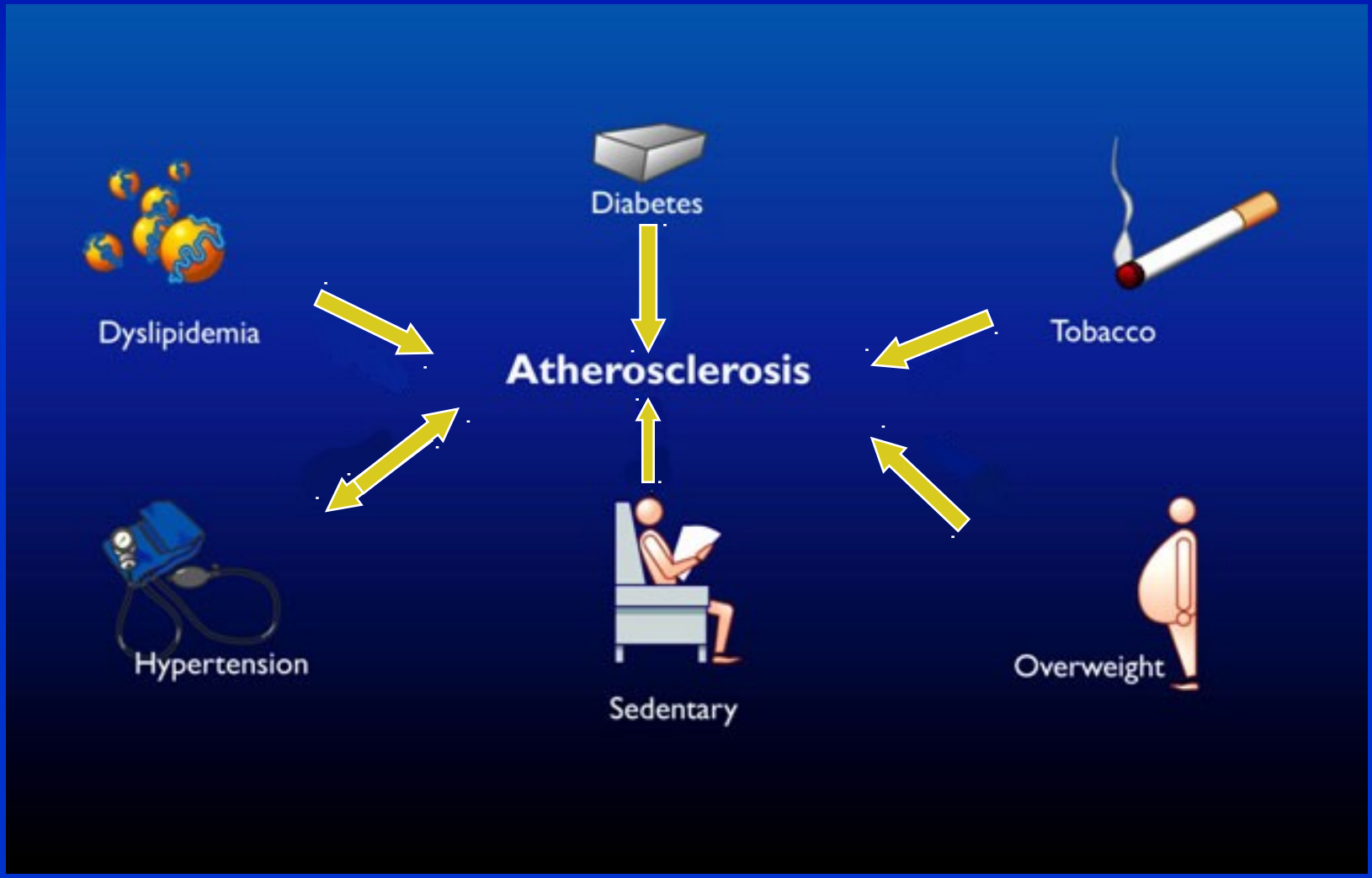


Source: Heart Disease and Stroke Statistics – 2005 Update.

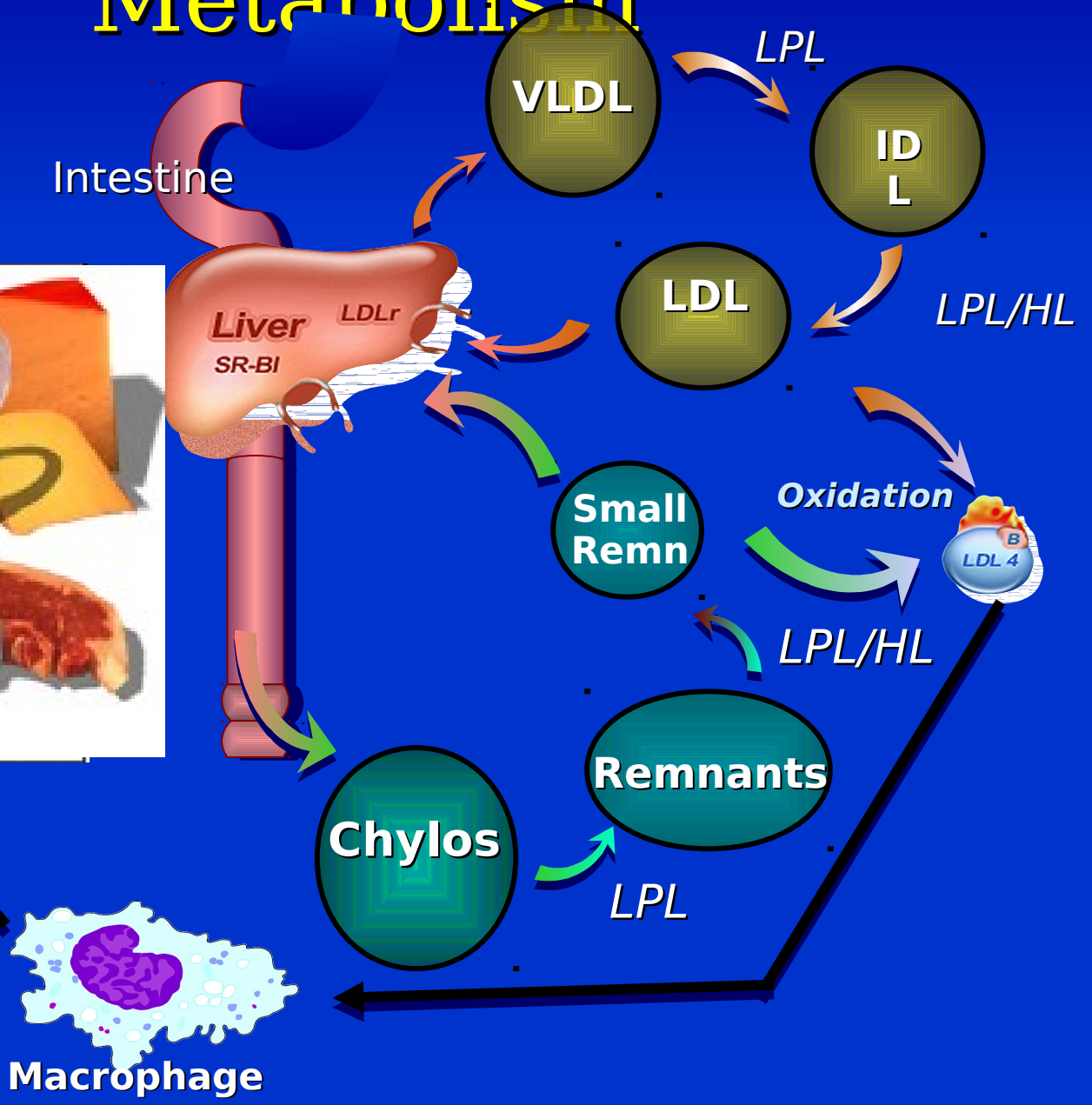
Dyslipidemia

Dyslipidemia: A disorder of lipoprotein metabolism, including lipoprotein overproduction or deficiency. Dyslipidemias may be manifested by elevation of the total cholesterol, the "bad" low-density lipoprotein (LDL) cholesterol and the triglyceride concentrations, and a decrease in the "good" high-density lipoprotein (HDL) cholesterol concentration in the blood.

Atherosclerosis



Model of Lipoprotein Metabolism



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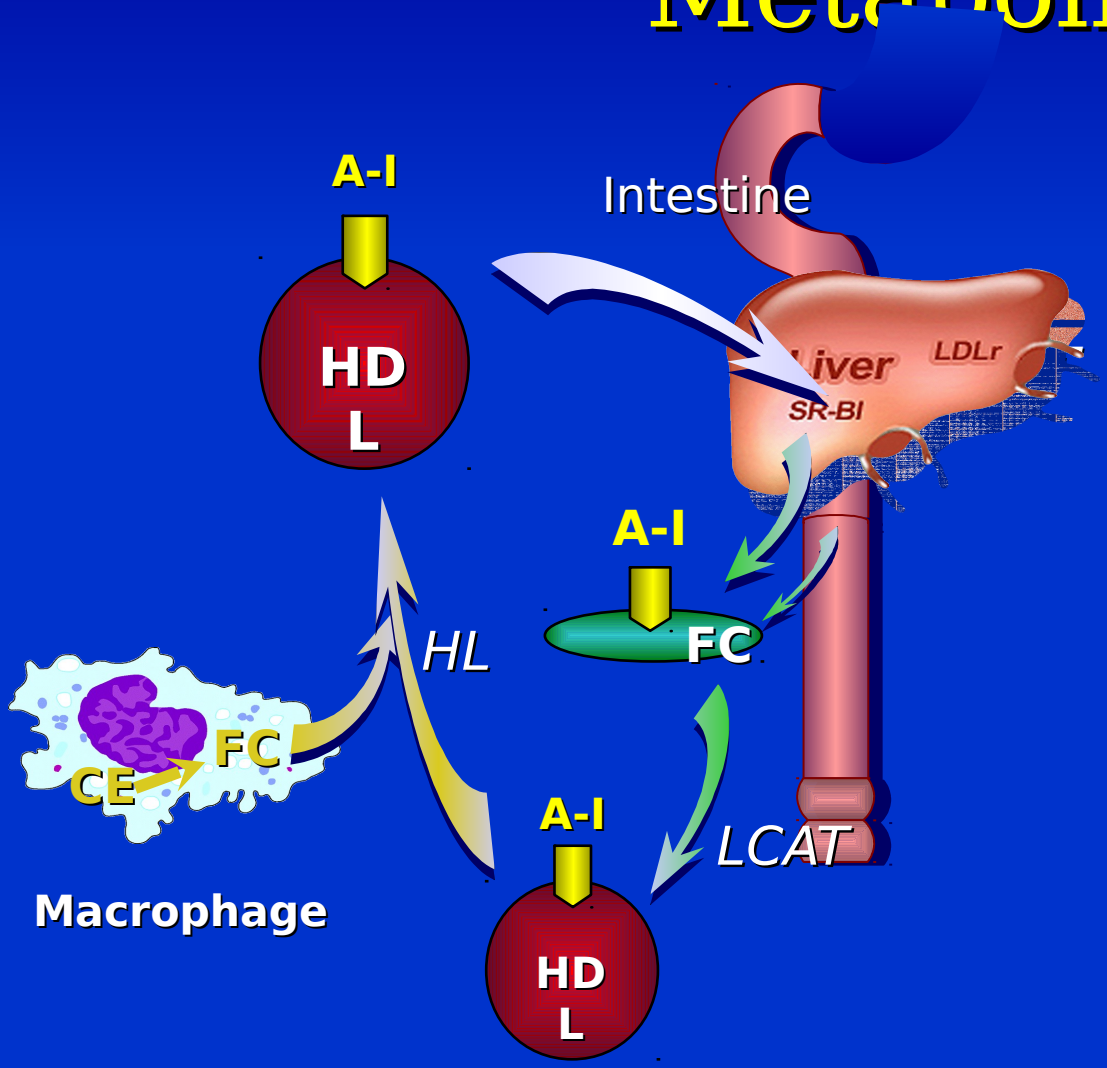
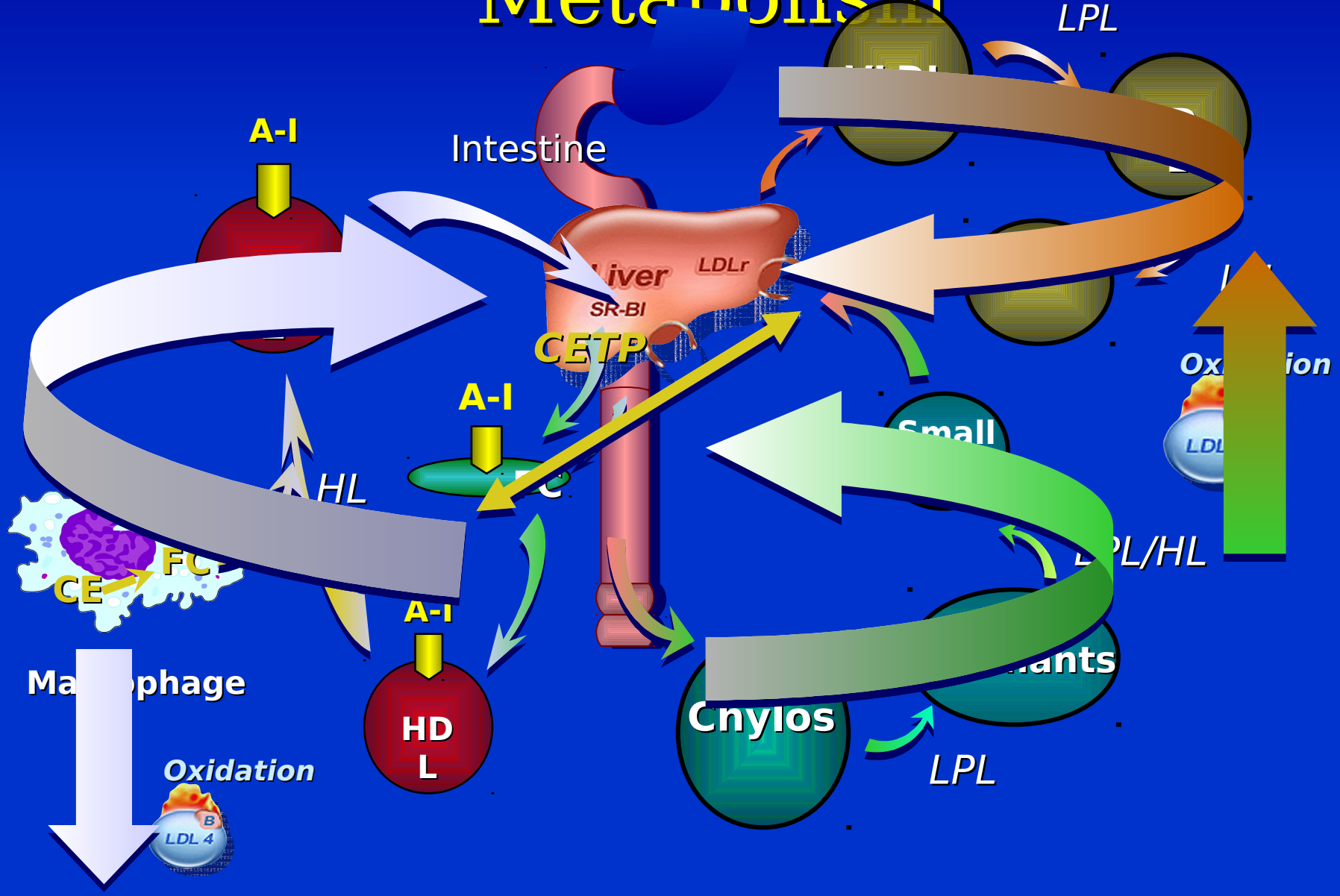


Model of Lipoprotein Metabolism



Normal lipid levels*

LDL CHOLESTEROL	
Less than 100	Optimal Goal
100 to 129	Close to Optimal
130 to 159	Borderline High
160 to 189	High
190 or higher	Very high (definite risk)
HDL CHOLESTEROL	
Less than 40	Low (High Risk)
60 or higher	High (Optimal)
TRIGLYCERIDES	
Less than 150	Optimal Goal
TOTAL CHOLESTEROL	
Less than 200	Optimal Goal
200 to 239	Borderline High
240 or higher	High

* NCEP recommendation

Hyperlipidemia classification

Fredrickson Classification of the Hyperlipidemias

Phenotype	Lipoprotein(s) elevated	Serum cholesterol concentration	Serum triglyceride concentration	Relative frequency, %
I	Chylomicrons	Normal to ↑	↑↑↑↑	<1
IIa	LDL	↑↑	Normal	10
IIb	LDL and VLDL	↑↑	↑↑	40
III	IDL	↑↑	↑↑↑	<1
IV	VLDL	Normal to ↑	↑↑	45
V	VLDL and chylomicrons	↑ to ↑↑	↑↑↑↑	5

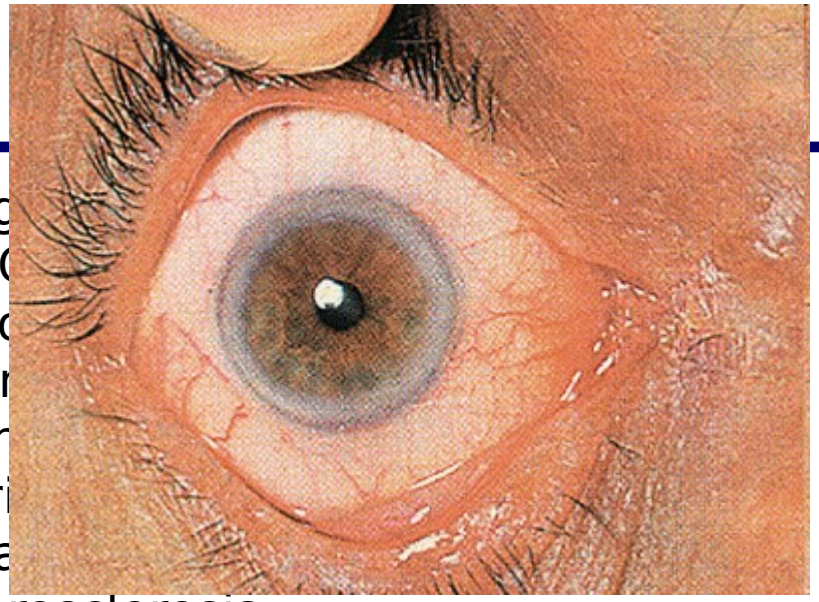
Familial
Hypercholesterolemia

Physical signs (not always present):

- Tendon xanthomas (thickening of tendons due to accumulation of macrophages filled with cholesterol).

- Xanthelasma palpabrum (yellowish patches above the eyelids)

- Arcus senilis corneae, whitish discoloration of the iris



- Ang
CAB
- Myo
- Tra
- Cer
- Peri
- A fa
atherosclerosis

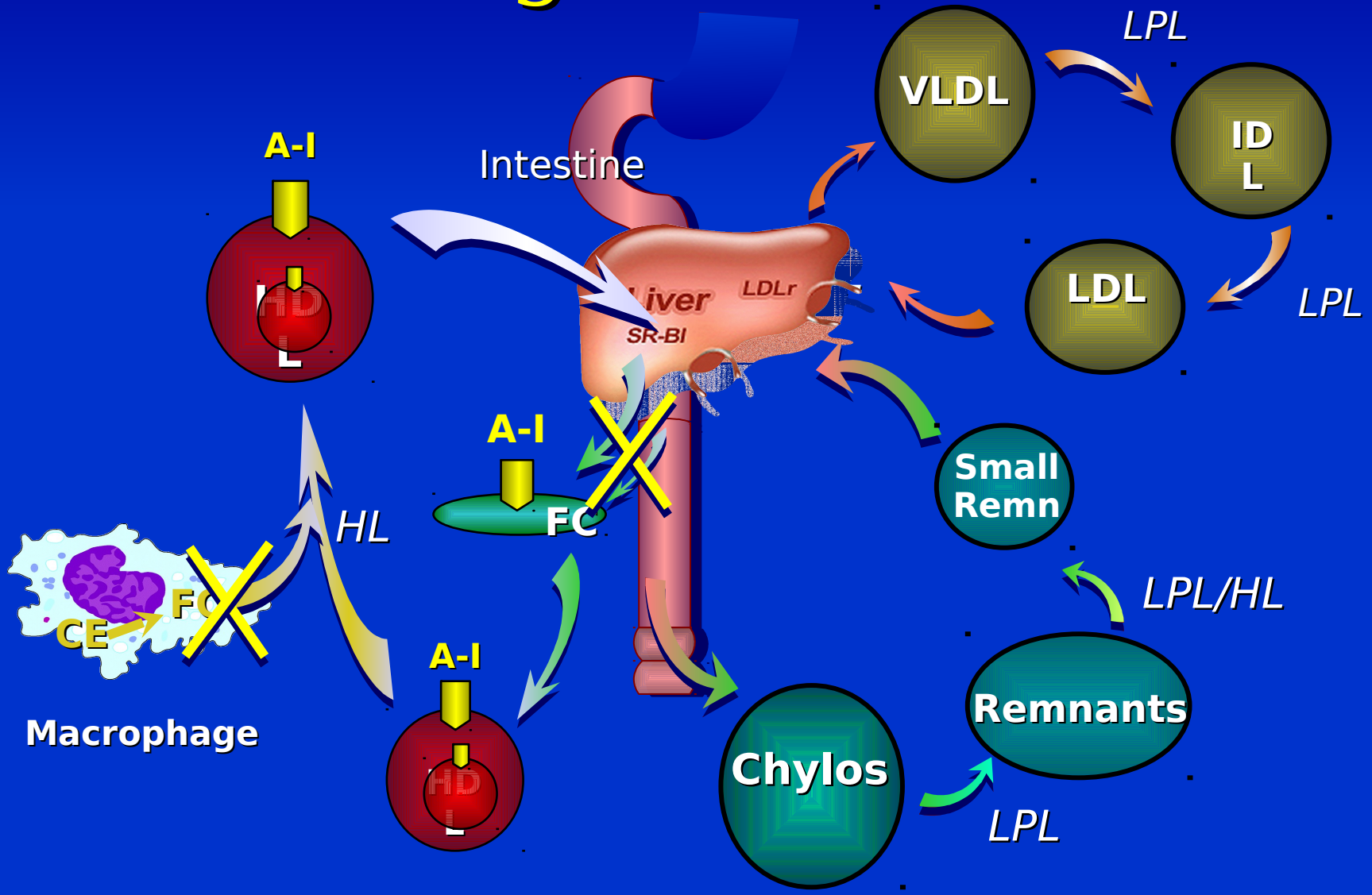
Fig. 2 – Tendinous xanthomas in the fingers in case 1, prior to ileal bypass surgery.

Small Remn

Chylo

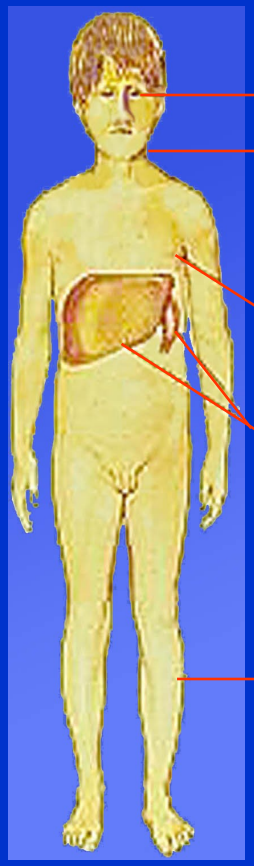
Fig. 1 - Xanthelasma - case 1.

Tangier Disease



Clinical Features of Tangier Disease

1. Excess Lipid Storage



Corneal Infiltration

Enlarged Orange Tonsils

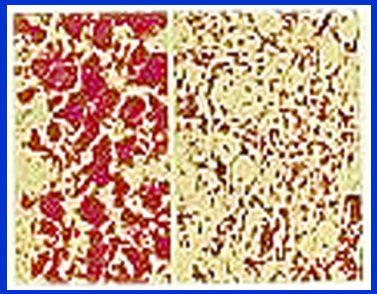
Lymphadenopathy

Hepatosplenomegaly

Peripheral Neuropathy

Tonsil

H & E Lipid Stain



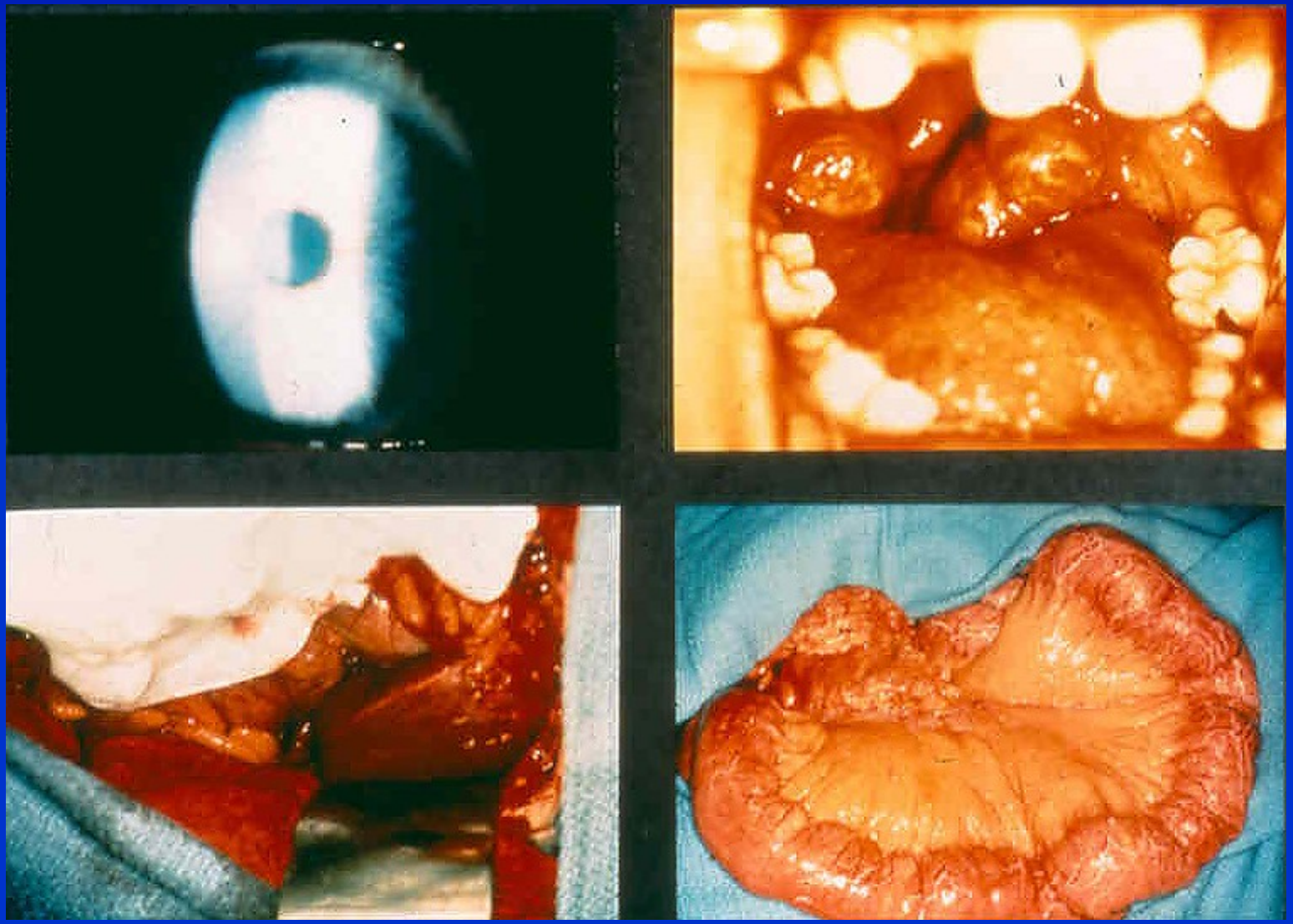
2. Marked Reduction of HDL-C

3. Hypercatabolism of apoA-1

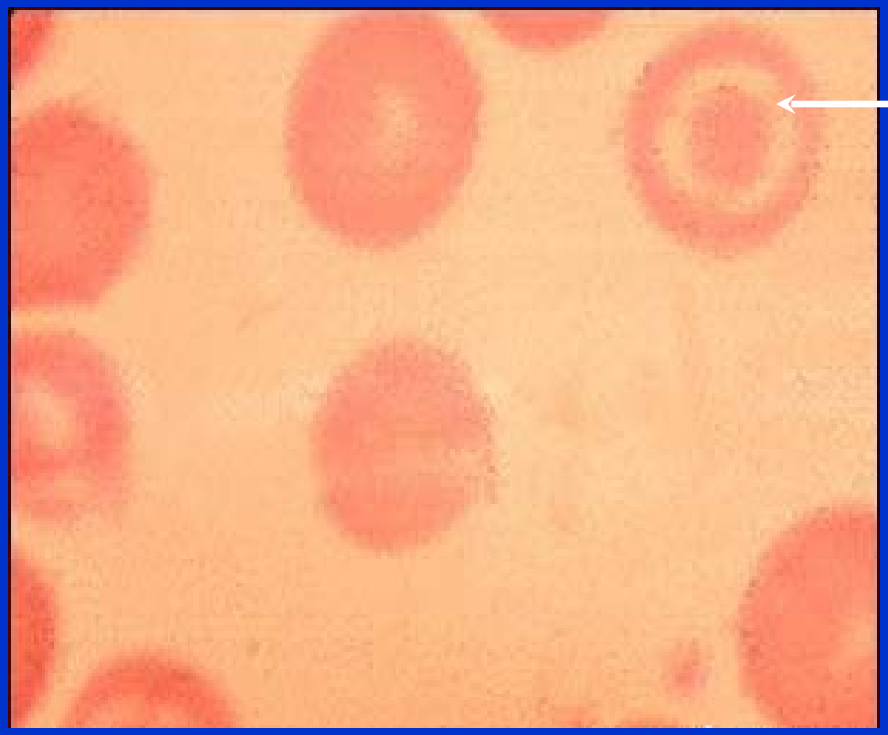
4. Decrease cell lipid efflux

D. Fredrickson, *et. al*. Ann Int. Med 55, 1016-1031 (1961)
B. Brewer, *et. al*. J Lipid Res 22, 217-228 (1981)

Clinical features of case

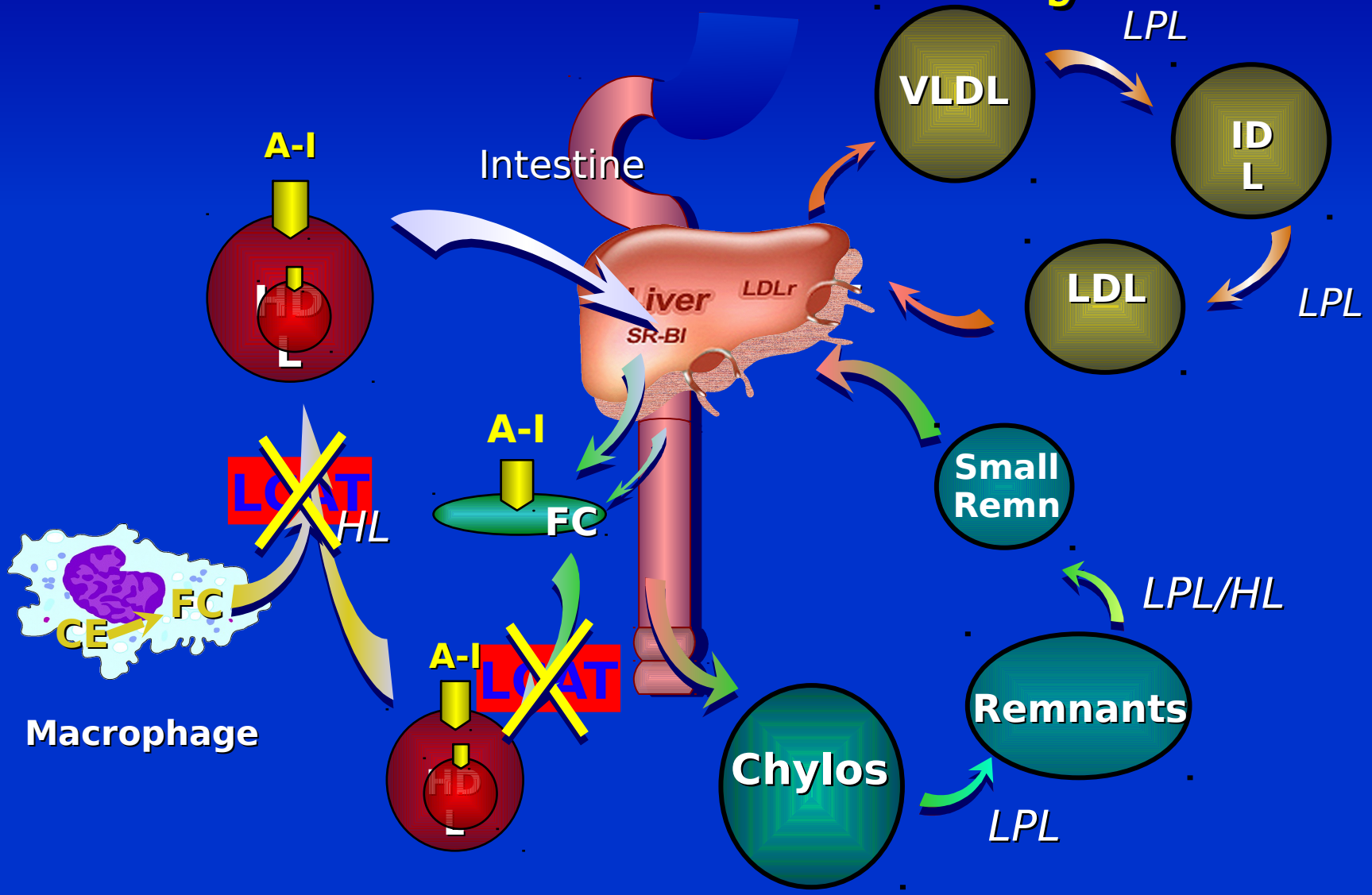


Blood smear of case



Target cell

LCAT deficiency



LCAT deficiency and Fish-eye Disease

- Both due to mutations in LCAT gene:
  - LCAT deficiency – complete
  - Fish-eye disease – partial
- Common to both types of LCAT deficiency:
  - Corneal arcus
  - Premature atherosclerotic vascular disease (rare)
- Unique to complete LCAT deficiency:
  - Proteinuria and progressive renal insufficiency

Photo of “fish eye”

Management of low HDL-C

- Therapeutic lifestyle changes
- Pharmacologic therapy
  - Statins
  - Fibrates
  - Niacin
  - CETP-inhibitors ?
  - HDL Infusion ?

ApoA-I Milano

- **ApoA-I mutation (R173C)**
- **Synonyms: Good HDL, Super HDL, Turbocharged HDL, Plaque buster HDL, Liquid Plumber HDL**
- **Acute IV therapy for Acute Coronary Syndrome**
- **Esperion Therapeutics-Pfizer**

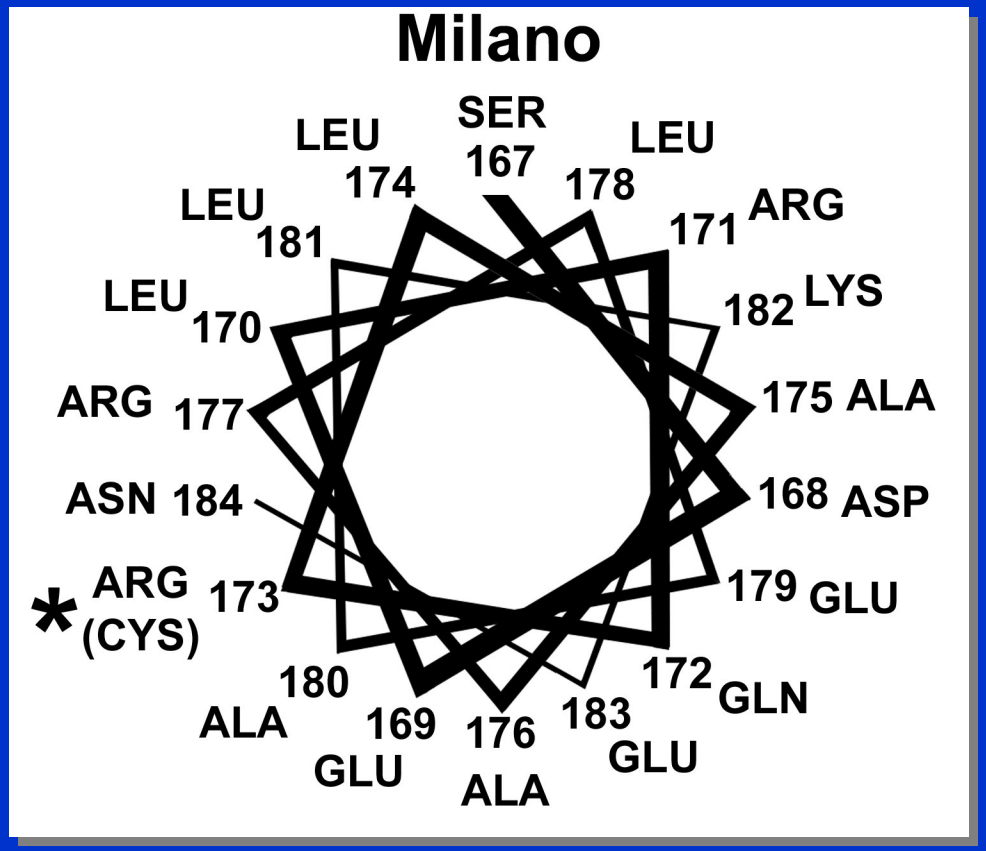
ApoA-I Milano

Limone Sul Garde,

Definition of ApoA-I Milano

ApoA-I Milano: A variant of apolipoprotein A-I identified in about 40 inhabitants of Limone sul Garde, a small town in rural North Italy, who had extraordinarily low HDL levels, levels so low that they were off the scale. Because HDL is the "good" cholesterol, it was expected that these people would have very high rates of heart disease. Instead, they seemed to be protected from heart disease and to enjoy longer lives than usual. The infusion of recombinant ApoA-I Milano-phospholipid complexes reportedly produces rapid regression of coronary artery atherosclerosis.

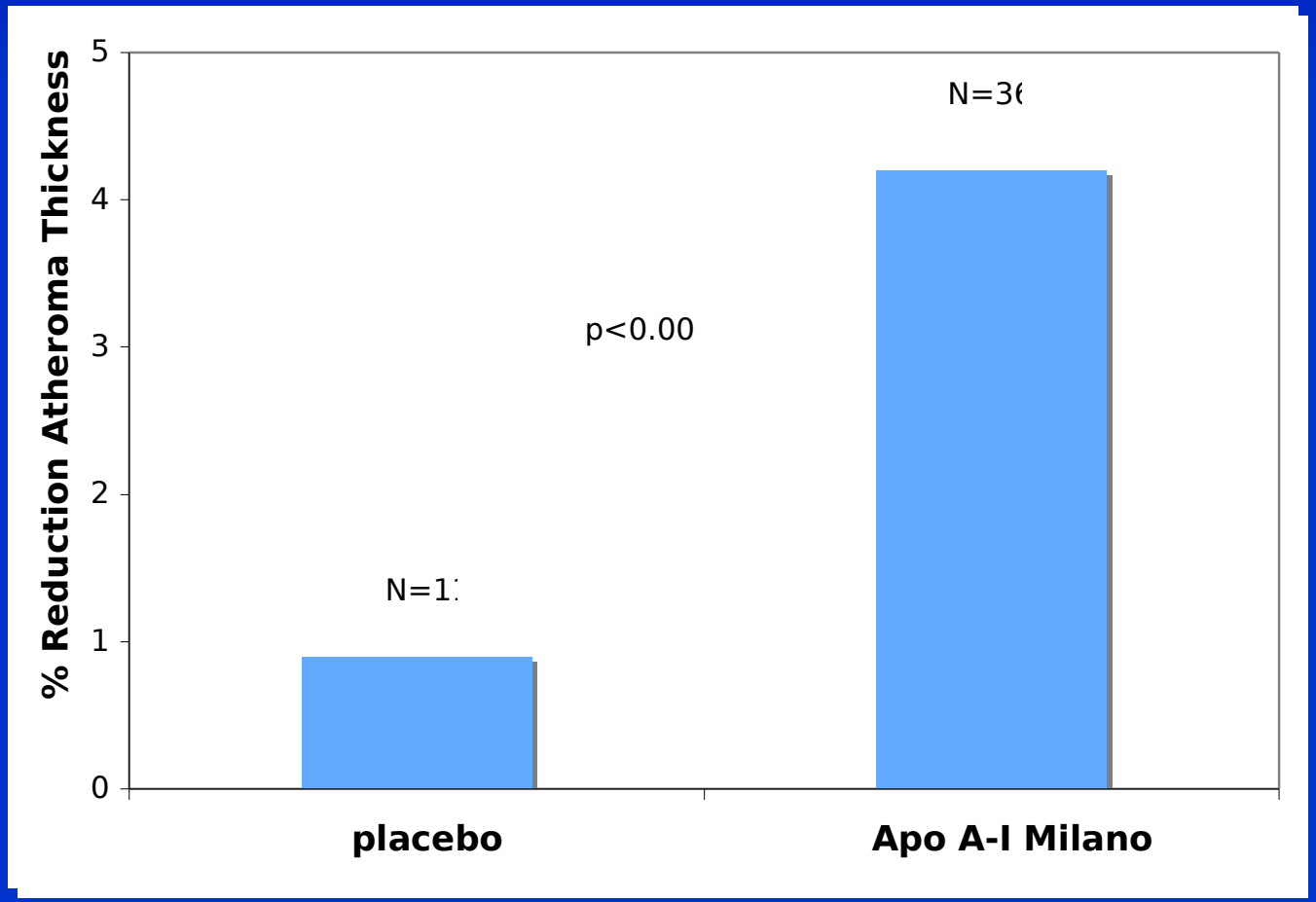
ApoA-I Milano structure



Clinical Trial apoA-I Milano

- **Multi-center double blind placebo controlled study**
- **N=123 Acute coronary syndrome**
- **IV infusion apoA-I Milano/phospholipid complex (1 infusion per week for 5 weeks).**
- **Assess coronary atherosclerosis by IVUS**

Clinical trial Apo-AI Milano for ACS



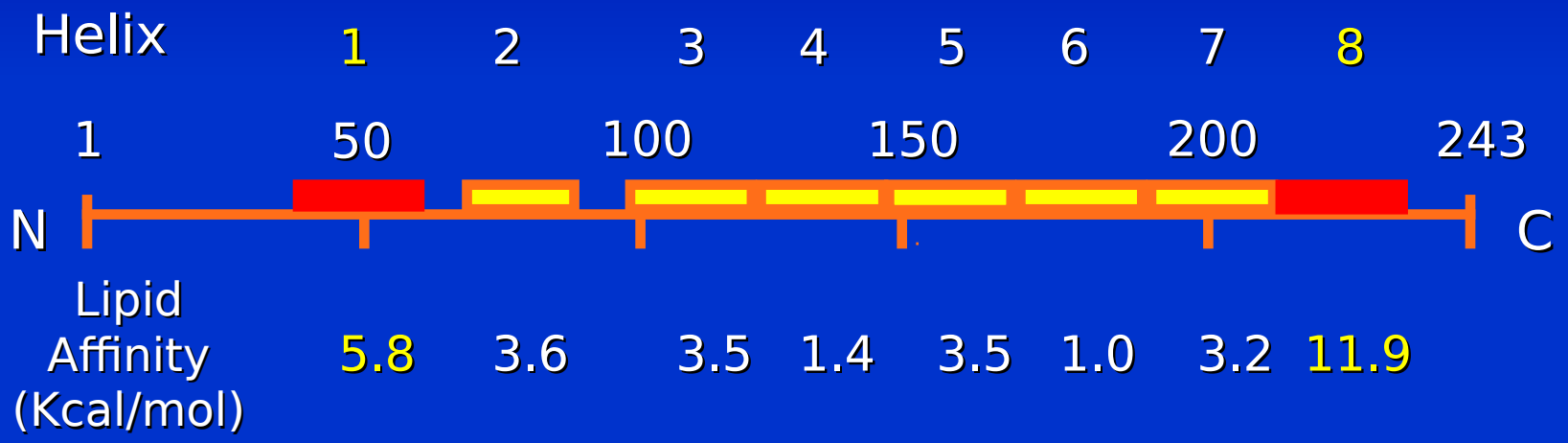
Nissen, S., *et al.* JAMA 290 (2003) 2292-2300

ApoA-I mimetic peptide 5A prevents the formation of atherosclerosis in ApoE deficient mice.

Marcelo J. A. Amar, M.D., Federica Basso, Ph.D., Steve Demosky, John Stonick, Alan T. Remaley, M.D.

National Heart, Lung and Blood Institute
Lipoprotein Metabolism Section

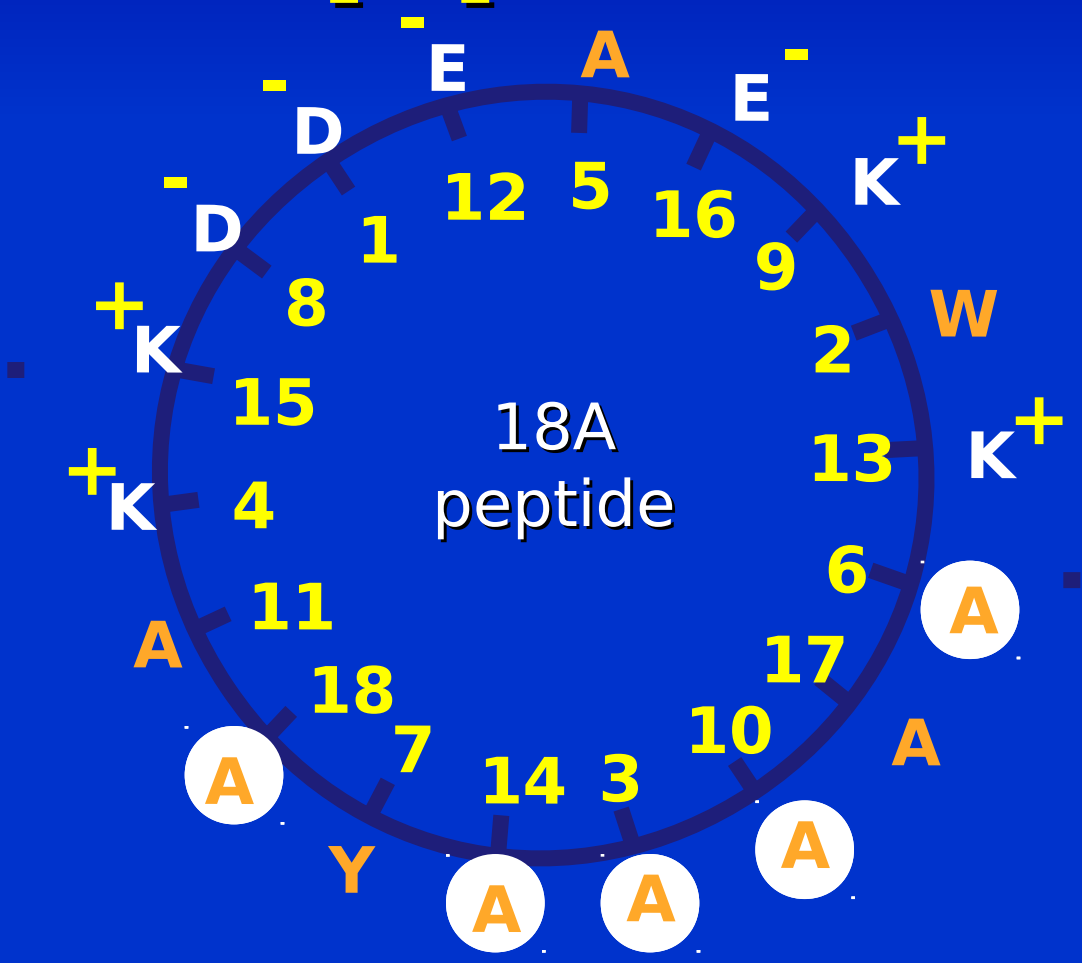
Secondary Structure of ApoA-I



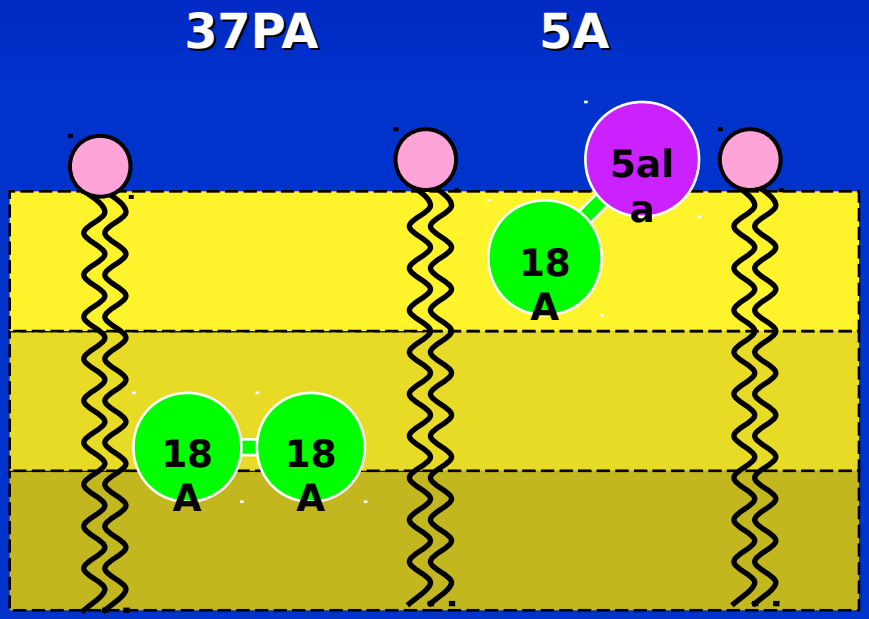
- Helix 1 and Helix 8 have the highest lipid affinity and are the only helices that can solubilize DMPC vesicles and promote lipid efflux from cells.
- The low lipid affinity helices work cooperatively with the two high lipid affinity helices in HDL formation and lipid efflux.

Gillote KL, *et al* JBC (1999) 274:2021, Mishra VK, *et al* Biochem (1998) 37:10313, Palgunachari MN *et al* ATVB (1996) 37:328, Natarajan P *et al*

5 Alanine residues were replaced from the original 18A peptide

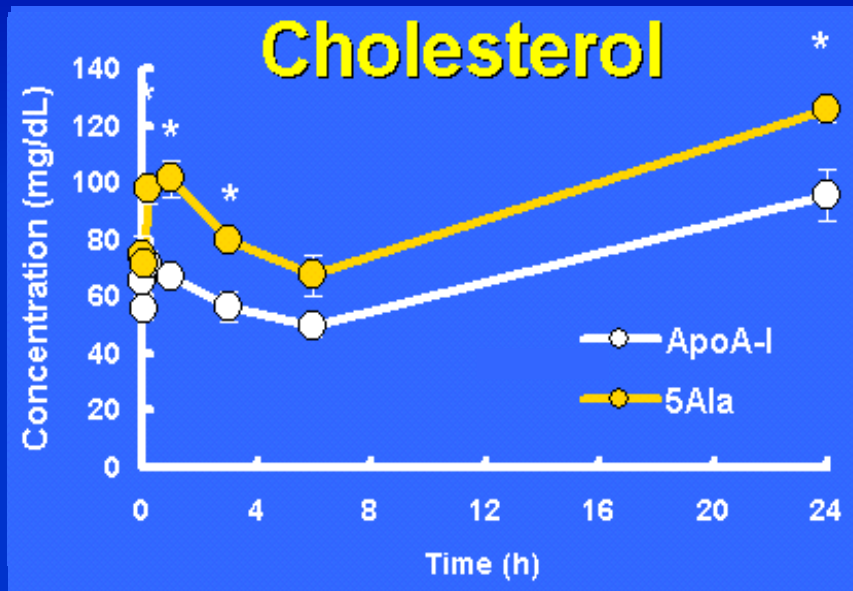


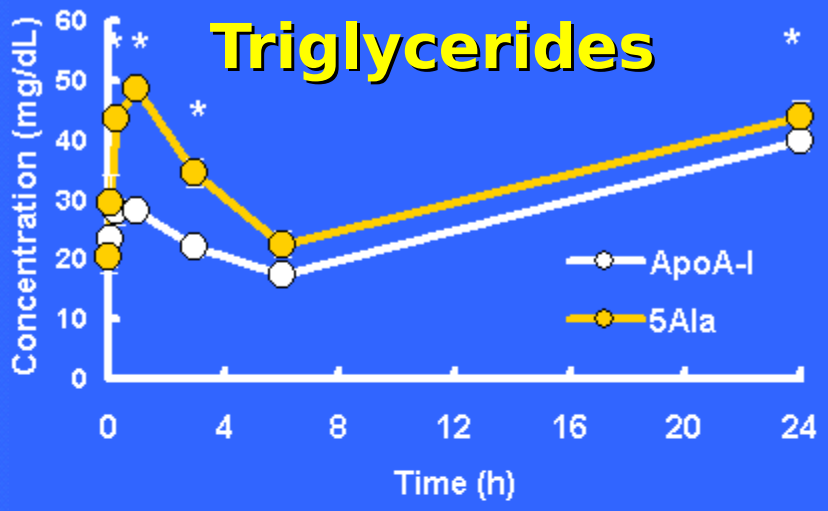
Model for How Peptide Function is Determined by its Depth of Penetration in Cell Membranes

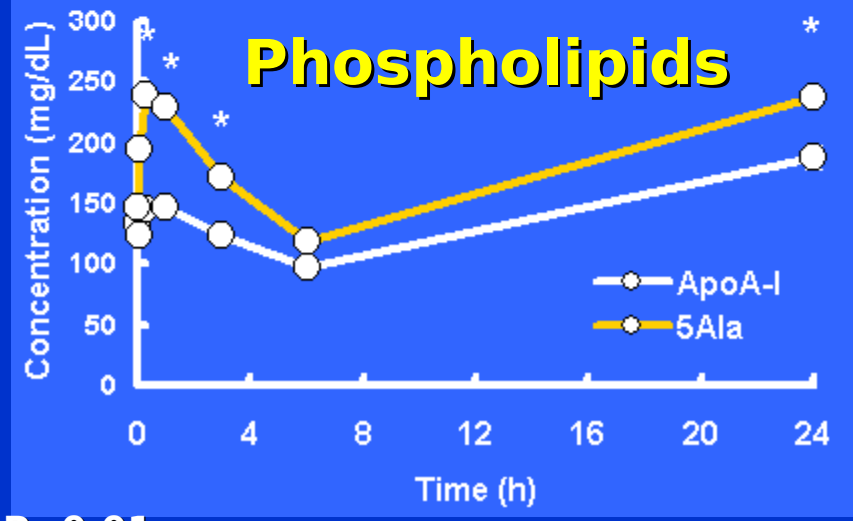


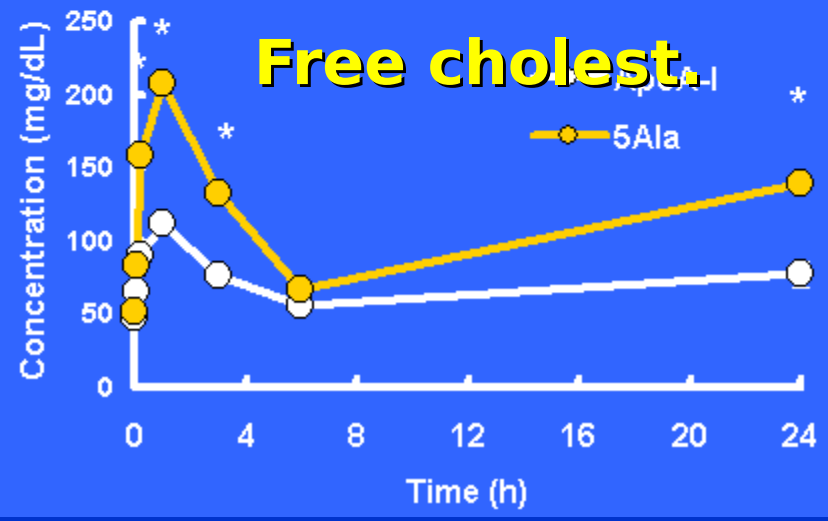
Zone	37PA	5A
ABCA1	+	+
Non-ABCA1	+	-
Cytotoxicity	+	-

Lipid changes in mice receiving 5A peptide are similar to the ApoA-I injected groups









P<0.01

Nine weeks of IP treatment with 5A led to

~~60% less atherosclerosis in apoE deficient~~

mice.